ROBERTS
PHARMACEUTICAL
CORPORATION

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room 6B-30
5600 Fishers Lane
Rockville, MD 20857

IND 25,512: Emitasol® (Metoclopramide) Nasal Spray
Serial #104: End-of-Phase II Meeting - Briefing Packet

Please refer to our request dated for an End-of-Phase II meeting and our subsequent telephone conversations with Ms. Melodi McNeil (HFD-180) confirming as the meeting date.

Based upon the Division's previous request, we are providing 10 copies of the pre-meeting packet. Additionally, we are providing a diskette (Word 6.0) with our questions to the Division.

The list of Roberts/Ribogene/GloboMax attendees for the meeting are as follows:

Roberts Laboratories Inc:
- David Haenick, Ph.D., Program Manager, Regulatory Affairs
- Alvin Howard, V.P., Regulatory Affairs
- Michael Petrone, M.D., V.P., Medical Affairs
- Edward Yau, Ph.D., Director, Toxicology
- David Tierney, M.D., Sr. V.P., Medical and Regulatory Affairs

Ribogene, Inc.:
- Laura Lehman, Ph.D., V.P., Research
- Frank Sasinowski, Esq., Hyman, Phelps, and McNamara

GloboMax, LLC:
- Gene Heyman, Ph.D., Director of Statistics
- Ruth Oliver, Ph.D., Senior Scientist, Pharmacokinetics
- Carol Trapnell, M.D., Medical Director
- David Young, Pharm.D., Ph.D., President and CEO

MERIDIAN CENTER II, FOUR INDUSTRIAL WAY WEST, EATONTOWN, NEW JERSEY 07724-2274 • TEL. (732) 389-1182 / FAX (732) 389-1014

Consultant:
Janice Gilden, M.D., Medical Consultant

The owner of the subject IND, Ribogene, Inc., per Ribogene's letter of has authorized Roberts to communicate with the FDA concerning this IND.

If you require any additional information or have any questions concerning this packet, please don't hesitate to contact me. We look forward to a productive meeting with the Division on

Sincerely,

David Haenick

David Haenick, Ph.D.
Senior Manager
Regulatory Affairs

Enclosures: FORM FDA 1571, Pre-meeting book
2 diskettes (1 archive, 1 desk copy for Ms. McNeil)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
Roberts Laboratories Inc.

2. DATE OF SUBMISSION

3. ADDRESS *(Number, Street, City, State and Zip Code)*
4 Industrial Way West
Eatontown, NJ 07724-2274

4. TELEPHONE NUMBER *(Include Area Code)*
(732) 676-1200

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Emitasol® (Metoclopramide) Nasal Spray

6. IND Number *(if previously assigned)*
25,512

7. INDICATION(S) *(Covered by this submission)*
Treatment of Diabetic Gastroparesis

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

DMF# 4877 (nds)
DMF# 4523 (nds)
DMF# 5813 (nds)
DMF# 4086 (nds facility)
DMF# 5713 (closure)
DMF# 4075 (resin)
DMF# 2434 (liner)
DMF# 3638 (screw on pump)

10. *IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 1 0 4

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR
☐ CLINICAL

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☒ OTHER End-of-Phase II Meeting Briefing Packet *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

- [X] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [ ] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [ ] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [ ] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [ ] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [ ] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [ ] YES [ ] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [ ] YES [ ] NO

The sponsor obligations that are transferred to the CRO will be submitted when the study is initiated.

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Michael Petrone, M.D.
Vice President, Medical Affairs

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVENT TO THE SAFETY OF THE DRUG

Michael Petrone, M.D.
Vice President, Medical Affairs

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
David Haenick, Ph.D. Senior Manager, Regulatory Affairs	David Haenick	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
4 Industrial Way West Eatontown, NJ 07724-2274	(732) 676-1200	

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

Metoclopramide Nasal Spray for Diabetic Gastroparesis
Study Synopsis

TRIAL NUMBER	*25,512-301R*
TITLE:	Comparison of the Efficacy and Safety of a New Intranasal Formulation of Metoclopramide versus Orally Administered Metoclopramide (Reglan®) in Patients with Diabetic Gastroparesis
OBJECTIVES:	Primary objectives: 1. To compare the efficacy of intranasal metoclopramide to orally administered metoclopramide for diabetic gastroparesis. 2. To compare the safety profile of intranasal metoclopramide to orally administered metoclopramide for diabetic gastroparesis. Secondary objectives: 1. To compare the pharmacokinetic/ pharmacodynamic relationship for intranasal and oral metoclopramide in patients with diabetic gastroparesis.
STUDY DESIGN:	The proposed study is a multi-center, randomized, placebo-controlled, double blind double-dummy phase 2/3 clinical trial
PLANNED SAMPLE SIZE:	250 evaluable patients will complete (approximately 125 patients per study arm)
TOTAL NUMBER OF CENTERS:	To be determined
PATIENT SELECTION CRITERIA:	Males and non-pregnant, non-lactating females diabetic patients ≥ 18 years of age with diabetic gastroparesis. Study patients will have documented autonomic neuropathy and a total symptom score of ≥ 6 on a 36-point Symptom Questionnaire (Symptom Questionnaire A, Appendix I).
STUDY MEDICATION:	Study patients will be randomized to receive either intranasal metoclopramide 20 mg four times a day (with meals and at bedtime) and an oral placebo OR oral metoclopramide 10 mg four times a day (with meals and at bedtime) with a placebo nasal spray. The duration of treatment will be 8 weeks.

MAIN PARAMETERS OF EFFICACY:	**Primary Efficacy Endpoint**
	• Change in total symptom score after eight weeks of treatment (refer to Symptom Questionnaire A, Appendix I)
	
	Secondary Efficacy Endpoints
	
	1. Improvement in Individual Symptoms
	
	• Symptom frequency and severity (refer to Symptom Questionnaire A, Appendix I):
	  • Change in total symptom score after each visit
	  • Change in each of the nine individual target symptom scores after each visit
	• Improvement in Symptoms (refer to Symptom Questionnaire B, Appendix II):
	  • Change in total improvement score after each visit
	  • Change in each of the nine individual target improvement scores after each visit
	
	2. Gastric emptying
	
	  • Gastric emptying at baseline and at week 8 of treatment

MAIN PARAMETERS OF SAFETY:	Adverse event monitoring is incorporated into each of the planned study visits. Main parameters of safety: • Incidence of total adverse events Incidence and severity of adverse events involving the nasopharynx. Investigators will perform a targeted nasopharyngeal assessment at each visit and complete an adverse event form as required. This assessment will incorporate both objective indicators (e.g., presence of erythema, edema, and ulceration of the nasal passages) and subjective reports (e.g., nasal itching, stinging, and tenderness) of toxicity

TREATMENT PERIOD:	All potential study patients will have a baseline evaluation including a medical history and physical examination, assessment of gastric stasis symptoms (refer to Symptom Questionnaire A, Appendix I), laboratory tests, and an assessment of the nasopharynx. Eligible patients will undergo a gastric emptying study prior to dosing. Dosing will begin on treatment day 1 with study patients returning to the clinical for assessments on weeks 2, 4, 6, and 8. These evaluations will involve reassessments of general health, assessment of frequency and severity of symptoms (Appendices I and II), a targeted assessment of the nasopharynx, and laboratory tests. A gastric emptying study will be repeated at study week 8. A study follow-up visit will occur 2 weeks after dosing for a final safety assessment (general health, a targeted assessment of the nasopharynx, and laboratory tests). On weeks 2 and 6, pharmacokinetic samples will be taken just prior to the morning dose. On weeks 4 and 8, they will be taken at least 30 minutes after the dose. Patients will also have at least one random pharmacokinetic sample taken 2-6 hours after a dose sometime during the treatment period.
STATISTICAL ANALYSIS: General:	The symptom assessment tool described by Perkel[1] will be used to assess symptoms and therapeutic efficacy before, during, and at the conclusion of treatment (Appendix I).[1] This tool asks patients to rate both the frequency and severity of each of nine target symptoms (early satiety, postprandial bloating, nausea, vomiting, meal tolerance, epigastric pain, heartburn, belching and regurgitation, and anorexia) over the preceding two week study period. Patients will be asked to assign each symptom a predefined ordinal frequency/severity score of zero to four. A total symptom score will be calculated as the sum of the severity/frequency ratings of the nine individual symptoms. During and at the conclusion of treatment, patients will also be asked to rate the level of improvement, or lack thereof, in each of their symptoms during the elapsed treatment period relative to their baseline

	(refer to Questionnaire B, Appendix II). They will assign a predefined ordinal score on a 7-point scale to each of the nine symptoms. A total improvement score will be calculated as the sum of the improvement ratings of the nine individual symptoms.
Sample Size Calculation:	The standard deviation of changes from baseline in the total symptom score was estimated to be 7.6 from a study published by Perkel.[1] Based on this estimate, 125 patients per treatment group will provide 80% power to reject the null hypothesis of a difference greater than or equal to 2.4, under the assumption that the two routes of administration are identical in their effect.
Analysis Plan:	<u>Primary Hypothesis</u> The primary objective of this study is to demonstrate that metoclopramide nasal spray is not inferior to metoclopramide oral tablets in the treatment of diabetic gastroparesis. In a prior three-week study, Perkel reported that metoclopramide oral tablets were shown to be superior to placebo in mean change from baseline in the total symptom score by 4.8 points.[1] Based on these results, 50% of this effect (2.4 points) was selected to be the equivalence margin for this study. Therefore, the primary statistical hypothesis is that the change from baseline (defined as the Week 8 assessment minus the baseline assessment) in the metoclopramide nasal spray treatment group is at least 2.4 points greater than that in the metoclopramide oral tablet treatment group. The alternative hypothesis is that the difference is less than 2.4 points. If the null hypothesis is rejected at the 5% level of significance, it will be concluded that the nasal spray is noninferior to the oral tablet, within a margin of 2.4 points. <u>Analysis of Primary Endpoint</u> Changes from baseline in total symptom score will be analyzed by a two-way analysis of variance (ANOVA) that includes the effects of treatment group and study center. The treatment group-by-

	center interaction will be assessed as an exploratory analysis. Analysis of Secondary Endpoints All secondary endpoints will be tested under the null hypothesis of no difference, to test for difference between treatment groups. Changes from baseline in total symptom score will be analyzed at Study Weeks 2, 4, 6, and 8 using the same ANOVA model as used for the primary endpoint. This will be done by using only available data, and by carrying forward results for all missed visits (Weeks 2, 4, and 6 only). Similar analyses will be done for the total improvement rating scores. Individual item symptom scores will be analyzed at each bi-weekly visit using the Cochran-Mantel-Haenszel procedure.[2] The cross-classification of baseline symptom score and study center will be used as the stratification variable, and the single degree of freedom test for trend will be extracted from the 2 x 5 contingency tables by assigning uniform scores to each response category. Individual item improvement rating scores will also be analyzed at each bi-weekly visit by the Cochran-Mantel-Haenszel procedure.[2] Study centers will be used as the stratification variable, and the single degree of freedom test for trend will be extracted from the 2 x 7 contingency tables by assigning uniform scores to each response category. Investigator and patient global assessments will be analyzed similarly. Subgroup Analyses Additional analyses of the primary endpoint will be performed to assess the effects of sex, age, race, as well as other relevant prognostic factors. Each of these analyses will be performed by an analysis of variance that includes the effects of treatment group, subgroup, and treatment group-by-subgroup interaction. Safety Incidence rates of all adverse events will be tabulated, counting only the first occurrence of each event.

	Incidence rates of patients discontinuing the study due to an adverse event will tabulated both overall and by specific event.
PHARMACOKINETIC/ PHARMACODYNAMIC ANALYSES:	Population pharmacokinetic analysis will be performed on the plasma concentration data collected in the trial. The objective of the analysis will be to: 1. Estimate the pharmacokinetic parameters of the nasal spray in target patient population; 2. Estimate the variability of the pharmacokinetic parameters; 3. Determine the influence of possible covariates (demographic, drug interactions, etc) on the pharmacokinetic parameters; 4. Estimate the relative bioavailability of the nasal spray to the oral tablet in patient population; 5. Estimate individual patient exposure The relationship between individual patient exposures, (estimated/evaluated in the pharmacokinetic analysis), will be investigated in the population PK/PD analysis. Duration of treatment and demographic covariates and their correlation with the PK/PD relationship will be examined. Change from baseline of the total scores on the two symptom assessment questionnaires (Appendices I and II) will be the dependent variables in separate models. Model building and validation will be performed using NONMEM and S-Plus software.